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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEWART A. CEDERHOLM-WILLIAMS

Appeal 2008-1157
Application 09/334,325
Technology Center 1600

Decided: February 4, 2008

Before DONALD E. ADAMS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of transforming cells, which the Examiner has rejected on grounds of lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

BACKGROUND

The Specification notes that "a wide variety of viral vectors have been selected or engineered for gene therapy. Moreover, nucleic acid can be delivered successfully without the use of viral vectors" (Specification 12). According to the Specification, "[s]imilarly, nucleic acid-based vaccines seek to induce a percentage of cells to produce immune-reaction inducing polypeptides, to induce an antibody-based or cellular-based immune response" (Specification 1). Separately, the Specification teaches that "[f]ibrin sealants are used to create solid formulations of polymerized fibrin or other fibrin-related molecules" (Specification 1).

Appellant teaches "compositions of fibrin sealants that incorporate recombinant vectors for delivery to a tissue or cell against which the sealant will be polymerized and, typically, adhered" (Specification 2). Appellant notes that with the use of fibrin sealants "the vectors can be maintained at a locally at [sic] high concentration in the solid gel produced by the sealant, thereby increasing the efficiency of transfection or transformation of cells" (Specification 2).

STATEMENT OF THE CASE

The Claims

Claims 1 and 13-16 are on appeal. Claims 13-16 have not been argued separately and therefore stand or fall with the representative claim. 37 C.F.R. § 41.37(c)(1)(vii). We will focus on claim 1 which is representative and reads as follows:

> 1. A method of transforming a cell comprising, in order, the steps of: applying a transformation effective amount of a nucleic acid to the cell; and adhering a pliable, adhesive

> fibrin gel to the cell so as to entrap the transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell and thereby transforming the cell with the nucleic acid.

The Examiner has rejected claims 1 and 13-16 under 35 U.S.C. § 112, first paragraph based on:

Donovan U.S. Patent 5,833,651 November 10, 1998

Schek et al., *Delivery and Protection of Adenoviruses using biocompatible hydrogels for localized gene therapy,* 9 Molecular Therapy 130-138 (2004) (hereinafter "Schek").

Deonarain, *Ligand-targeted receptor-mediated vectors for gene delivery*, 8 Expert Opinion on Therapeutic Pat. 53-69 (1998) (hereinafter "Deonarain").

Verma and Somia, *Gene therapy – promises, problems and prospects*, 389 Nature 239-242 (1997) (hereinafter "Verma").

Stephen L. Eck and James M. Wilson, *Gene based Therapy*, *in The Pharmacological Basis of Therapeutics*, 77-101 (1996) (hereinafter "Eck").

Gorecki, *Prospects and problems of gene therapy: an update*, 6 Expert Opinion on Emerging Drugs 187-198 (2001)(hereinafter "Gorecki").

The Issue

The Examiner's position is that the

> specification fails to provide adequate guidance and evidence for transforming a cell in vitro or in vivo by applying a nucleic acid, such as a vector or a virus carrying the nucleic acid, to the cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell in vitro or in vivo at any location of any subject via various administration routes.

(Answer 4.) The Examiner concedes that the "method as taught by Don[o]van to transform a cell in vivo is enabled, however, the method to transform a cell in vivo as claimed in the instant invention, which is different from the method taught by Don[o]van and by the state of the art, is not enabled" (Answer 12).

According to the Examiner, undue experimentation would be required because the claimed invention "must provide such a high concentration of the vector in order to increase the efficiency of the transformation of the cells in vitro or in vivo in the claimed invention" (Answer 15).

Appellant responds that the

> rejection suggests that Appellant's invention must "increase or enhance cell transformation efficiency". That is not a requirement of the patent law either. The rejection further indicates that Appellant must show every possible way to administer his invention. And that is not a requirement of the patent law. Accordingly, Appellant submits that this rejection, whether under 35 U.S.C. §112 or §101, is without merit.

(App. Br. 4.)

In view of these conflicting positions, we frame the issue before us as follows:

Would undue experimentation have been required to apply the nucleic acid prior to application of the fibrin gel in order to result in transfection of the nucleic acid into the cells?

FINDINGS OF FACT

1. Donovan teaches that a "stent can be loaded with virus by mixing the monomer solution of the first polymer composition with virus or

by directly applying the virus to the polymerized composition" (Donovan, col. 13, ll. 10-13).

2. Donovan claims a "method for delivering nucleic acid to cells . . . comprising the steps of: providing a stent comprising . . . a first polymer composition comprising fibrin . . . and virus comprising nucleic acid associated with the first polymer composition wherein the stent is capable of delivering nucleic acid to cells" (Donovan, claim 21 and col. 20, ll. 36-45).

3. Donovan notes that over "14 days, the stents released approximately 50% of the loaded titer with the greatest release from about 1 to about 3 days. The functionality of this virus was confirmed by infecting aortic smooth muscle cells and demonstrating transgene function" (Donovan, col. 18, ll. 22-26).

4. Donovan cites U.S. Patent 5,510,077 to Dinh on incorporation of drugs into fibrin coated stents (*see* Donovan, col. 15, ll. 57-60).

5. Schek teaches "we implanted virus containing hydrogels in the quadriceps muscles of mice. We also implanted virus suspended in liquid to serve as a comparison." (Schek, p. 134, col. 1 and 2).

6. Schek teaches that the "volume of the ossicles that were formed using virus in fibrin was significantly larger than that of those formed using either collagen or liquid" (Schek, p. 134, fig. 5 legend).

7. Schek teaches that "[i]n vitro infection data demonstrated that virus released from either gel was at least as effective as virus suspended in liquid medium at transducing cells" (Schek, p. 134, col. 2).

8. Eck teaches "[a]s of 1995, three gene transfer systems (retroviral vectors, adenoviral vectors, and liposomes) had been used in human gene therapy" (Eck, p. 83, col. 1).

9. Eck identifies a number of factors relevant to gene therapy, including efficiencies in distribution of vectors, uptake of vectors and expression of nucleic acids and proteins once inside cells (*see* Eck, p. 82, col. 1).

10. Verma teaches that as of 1997, there was no successful gene therapy outcome (Verma, p. 239, col. 1).

11. Verma teaches that the "Achilles heel of gene therapy is gene delivery . . . the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Verma, p. 239, col. 3).

12. Deonarain recognizes that "this approach to gene delivery is much less efficient than viral gene delivery. However, under optimal conditions, enough gene product may be produced to give a therapeutic benefit" (Deonarain, p. 65, col. 1).

Discussion

There is no dispute that both the Specification and prior art teach mixtures of fibrin and nucleic acid which will function to transform cells (FF 1-7). One argument relates to the scope of the phrase "applying a transformation effective amount of a nucleic acid to the cell" in claim 1. The Examiner contends that the scope of "applying" in claim 1 will "encompass transforming cells in vivo via various administration routes, such as intravenous administration, intraperitoneal administration, oral

administration, subcutaneous administration, and intramuscular administration" (Answer 6).

In analyzing the phrase "applying a transformation effective amount of a nucleic acid to the cell" in claim 1, our mandate is to give claims their broadest reasonable interpretation. "During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow." *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989).

Regarding the "applying" phrase, the Specification teaches that the method can be performed ex vivo (*see* Specification 2, ll. 28-31). Among the different ways to "apply" that might fall within the scope of the claims, the Specification teaches that the method can be performed by "surgically exposing the tissue to allow for the applying steps" (Specification 3, ll. 7-8). The Specification teaches performing surgery on an animal and exposing the tissue in order to perform the application step (*see* Specification 3, ll. 9-15). The Specification teaches forming recombinant cells which are then implanted into animals (Specification 4, ll. 8-13). Lastly, the Specification contemplates spraying the nucleic acid and the sealant onto the recipient surface (Specification 17, ll. 28-31). The Specification recognizes that the sealant mixture is pliable for 30 seconds or less (Specification 17, ll. 16-17).

A reasonable construction of the "applying" phrase of claim 1 in light of the teachings of the Specification is that there must be a direct application of the nucleic acid and then the fibrin to a cellular target. One of the Examiner's concerns appears to be the indirect application of the nucleic acid followed by subsequent administration of the fibrin, for example that the nucleic acid is introduced intravenously and targeted to a cell type by

known techniques and then the fibrin is introduced and is unable to target to the same location to which the nucleic acid was addressed.

However, the Specification never teaches or contemplates indirect application modes. Further, the ordinary practitioner would not interpret "applying" as including intravenous administration since the practitioner would recognize that introducing fibrin into the bloodstream would cause a clot, which would be expected by the ordinary practitioner to result in stroke, cardiac arrest or other undesirable sequelae. With regard to the other modes of administration listed by the Examiner, either surgical incision or sequential spraying of the components with a spray head as envisioned by the Specification would permit some forms of intraperitoneal administration, oral administration, subcutaneous administration or intramuscular administration, and the ordinary practitioner would immediately recognize that some modes of administration would result in undesirable morbidity and mortality (*see* Specification, p. 17, ll. 8-19). *See Atlas Powder Co. v. E.I. du Pont De Nemours & Co.,* 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude ... possible inoperative substances....'").

We have no reason to doubt the Examiner's assessment of the state of the art in general, and we think it is fair to say that the field of gene therapy is indeed recognized as highly unpredictable by those of skill in the art (*see* Answer 8). However, we are not persuaded by the Examiner's argument that the "claims read on applying a nucleic acid to cells in vivo so as to transform cells and the transformation of cells in vivo must have a use,

which is to provide therapeutic effect in vivo" (Answer 8). We interpret the Examiner's argument as an attempt to interpret the claims to require an in vivo therapeutic effect from the current claims. First, this argument would be more properly raised as a scope of enablement issue. Second, both the claim and the art cited by the Examiner do not support the conclusion drawn in the rejection. The claim is broadly drawn to transforming cells and no therapeutic benefit is required in the claim. The claim encompasses transformations done in vitro, ex vivo and in vivo. While the Examiner does not concede that the method would function in vitro or ex vivo, there is no scientific reasoning or evidentiary support in the Answer for the proposition that ordinary infection of tissue culture plates with viruses, or calcium phosphate transformations, or other known in vitro or ex vivo transformation methods would be negatively impacted by spraying fibrin on top of the transformation mixture. There is evidence that fibrin will not impact infection when premixed with the virus (FF 1-7). Therefore, we disagree with the Examiner's intimation that there is no use for the claimed invention. The scope of the claimed invention encompasses in vitro and ex vivo utilities that would be clearly expected to function according to the claimed invention.

We also disagree with the Examiner's argument that "[t]here is no evidence of record that shows increased or enhanced efficiency of cell transformation by the claimed method either in vitro or in vivo via various administration routes" (Answer 12). This argument, repeated through the Answer, presupposes that there is a requirement for the invention to have improved or enhanced efficiency (*see, e.g.,* Answer 14-15). However, the

Federal Circuit has noted that "[f]inding that an invention is an 'improvement' is not a prerequisite to patentability. It is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability." *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.,* 807 F.2d 955, 960 (Fed. Cir. 1986).

Also, the art cited by the Examiner does not support a conclusion that gene transfer will not occur during in vivo administrations following the disclosure of the method (*see* FF 8-12). At best, the art cited demonstrates that therapeutic gene therapy is unpredictable and would require undue experimentation (*see* FF 10-11). If the claim were drawn to therapeutic gene therapy, or included a step or steps which required some therapeutic benefit, this argument might have some significant force. However, while the claims broadly encompass therapeutic gene therapy and the Specification contemplates in vivo therapeutic gene therapy, this is only one of the uses of the claimed method (*see* Specification 3, ll. 3-25). Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response. *See In re Cortright*, 165 F.3d 1353 (Fed. Cir. 1999) (claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair).

In addition, the post filing date art cited by the Examiner demonstrated some therapeutic effect, in that intramuscular injection of a liquid containing a viral vector functioned to transform cells and induced ossicle formation (*see* Schek, p. 134, col. 2). Schek also demonstrated that when the liquid containing virus was premixed with fibrin, the level of bone formation increased (*see* Schek, fig. 5). We find that the ordinary

practitioner would therefore expect that if liquid containing the virus alone functioned in transformation, and fibrin mixed with liquid functioned better, that the method where liquid is injected first and the injection site is then coated with fibrin would reasonably be expected to work at least as well as liquid alone, even if not as well as when premixed with fibrin. This evidence of Schek contradicts the Examiner's enablement position, since it shows that in vivo, the transformed virus functioned to cause a significant biological effect (*see* Schek, p. 134, col. 2).

Based on the above, we conclude the Examiner has not made a prima facie case of lack of enablement under 35 U.S.C. § 112, first paragraph (FF 1-12).

CONCLUSION

In summary, we reverse the rejection of claims 1 and 13-16 under 35 U.S.C. § 112, first paragraph.

REVERSED

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